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NEPHROLOGY FORUM

Diabetic nephropathy: Strategies in prevention and management

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Case presentation

A 33-year-old man received a cadaveric renal transplant at New England Medical Center (NEMC). He first developed insulin-dependent diabetes mellitus at age 11. Over the ensuing 22 years his diabetes was complicated by diabetic retinopathy that required multiple laser photocoagulation treatments and a vitrectomy of the right eye in 1974. Peripheral neuropathy produced sensory deficits in all extremities, and he had a "silent" lateral wall myocardial infarction; he had no episodes of diabetic ketoacidosis or infection.

One and one-half years earlier he had been admitted to a local hospital because of fatigue, weakness, and poorly controlled diabetes. He was reported to have renal insufficiency and hypertension at that time and was discharged after his diabetes was better controlled. Over the following year he was hospitalized 7 times for poorly controlled hypertension and congestive heart failure. Renal function progressively deteriorated, and maintenance hemodialysis was initiated 6 months before admission to NEMC. He was subsequently stable; both the diabetes and hypertension were well controlled, and the patient had no episodes of congestive heart failure or angina during thrice-weekly hemodialysis treatments of 5 hours each and while taking 40 units of NPH insulin daily, phosphate binders, and multivitamins. He did have one episode of uremic pericarditis, which was treated with increased hemodialysis and antiinflammatory drugs.

Shortly after starting hemodialysis, he was evaluated at NEMC. He had no suitable prospective living related donor and was placed on the cadaveric transplant list 2 months after hemodialysis was begun. Six months later he received a 4/4 HLA antigen-matched kidney. Postoperatively, the graft functioned well and the patient's urine output was 3 to 4 liters per day. The only initial problem was a widely fluctuating blood sugar level that ranged from 46 to 504 mg/dl and required frequent adjustments of his insulin dose. On postoperative day 2 his temperature rose to 38.5° C. Thorough investigation over the next several days revealed no source of infection. His graft continued to function well and the BUN and serum creatinine levels fell to 48 mg/dl and 2.3 mg/dl by the sixth postoperative day. He had daily fevers of 38° to 39° C, but no source of infection could be found and no antibiotics were given.

On the seventh postoperative day, the serum creatinine level rose to 3.6 mg/dl and urine output fell. He was treated with "pulse" doses of steroids and graft irradiation for presumed acute rejection. He did not respond to this anti-rejection regimen and the serum creatinine level continued to rise. A second steroid pulse was considered but not administered because his transplant rejection was believed irreversible. His steroid and immunosuppressant drugs were tapered starting on the 14th postoperative day, and hemodialysis was reinstituted. A transplant nephrectomy was to be done on the 15th postoperative day, but during induction of anesthesia the patient developed complete heart block followed by ventricular tachycardia and fibrillation. He was quickly resuscitated, and an electrocardiogram revealed inferior ischemic changes. Hemodialysis was reinstituted after cardiac enzyme studies showed no myocardial injury. One week later the patient underwent successful transplant nephrectomy and A-V fistula repair. The remainder of his hospital stay was uneventful except for severe depression, and he was discharged on the 31st postoperative day.

He returned to his local dialysis unit for continued maintenance hemodialysis. He was extremely depressed and manifested poor adherence to fluid and dietary prescriptions with frequent episodes of volume overload. Six weeks following discharge from NEMC he died en route to his local hospital, presumably because of acute myocardial ischemia with fluid overload.

Discussion

DR. ELI A. FRIEDMAN (*Professor of Medicine, and Chief, Renal Disease Division, Downstate Medical Center, Brooklyn, New York*): About one-half of type-I diabetics (formerly termed juvenile diabetics), develop renal failure in a mean of 20 years. At present, approximately one in four patients beginning therapy for end-stage renal disease (ESRD) in the United States is diabetic. Diabetics face a more morbid course during dialytic therapy as well as after kidney transplantation, and they have a substantially greater mortality rate than do age- and sex-matched nondiabetics. We can estimate the magnitude of the economic burden of diabetic nephropathy by dividing the yearly

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federal cost for the ESRD program in 1981, which was about $1.4 billion, by four; thus, the United States spends a minimum of $300 million annually on diabetics with uremia. But, because diabetics require more physician care, and longer and more frequent hospitalizations than do nondiabetics, the cost for their treatment is even greater than this minimum estimate.

In analyzing the course of the patient under consideration today, I will review the natural history of renal damage in diabetes and then discuss therapeutic options once uremia supervenes. Finally, I will present evidence suggesting that glomerulopathy is induced by hyperglycemia and therefore may be prevented if blood sugar is maintained at normal levels.

The story of the patient under discussion today began, as is not unusual in type-I diabetics, with his 20th year of insulin dependence, when he was hospitalized for renal insufficiency and hypertension. It is stated that when he was discharged from the hospital, his diabetes "was better controlled," although we are provided with no specific documentation that this was so. Successful regulation of blood glucose in insulinopenic and ketosis-prone type-I diabetics was, in the past, more art than science. If one were to poll any group of physicians concerning their concepts of the limits of "good control" of diabetes in a patient with type-I diabetes, the wide range of responses would illustrate the extent of confusion and imprecision regarding appropriate management of this disease. Whereas the selection of therapeutic approaches made little difference in the past because none was both efficacious and practical, recent technical advances have made it possible to achieve sustained euglycemia for many patients. Most important, had this patient received from the onset the kind of treatment now available for newly diagnosed diabetes, his multiple complications might well have been prevented. I will attempt to support this conjecture later.

Diabetics risk developing renal complications from many different causes, as noted in Table 1. I will not discuss the severe consequences of urinary tract infection that affect diabetics except to observe that each of 5 patients with renal abscesses whom I have treated have been diabetics. Similarly, although renal papillary necrosis does occur in ethanol and analgesic abusers and in patients with sickle trait, the majority of patients with this complication in my experience have been type-I diabetics.

Natural history of diabetic renal disease. Our knowledge of the natural history of diabetic nephropathy is restricted to type-I diabetes. We can only speculate that the sequence of pathologic events is similar in the type-II variety (previously called maturity-onset diabetes). Difficulty in establishing a date of onset of hyperglycemia and the paucity of sequential renal biopsies in patients with type-II diabetes preclude more than a guess as to the correlation between severity of microvasculopathy and altered renal function. Glomerulosclerosis, the renal lesion characteristic of diabetic microangiopathy, is found in uremic patients with both types I and II diabetes (Fig. 1).

Kimmelstiel and Wilson, in a retrospective autopsy study of 8 diabetics aged 48 to 63 years, first detected nodular intercapillary glomerulosclerosis more than 40 years ago [1]; this finding is now recognized as a specific lesion that is present in about one-half of all diabetics. The more prevalent, diffuse form of intercapillary glomerulosclerosis was described more recently; this lesion can occur alone or in conjunction with nodular glomerulosclerosis. The earliest change in glomerulosclerosis is an increase in mesangial matrix and thickening of the glomerular basement membrane (GBM) (Fig. 2). When type-I diabetes is first diagnosed, renal biopsies do not show ultrastructural thickening of the GBM. This finding, albeit a negative one, is important in refuting the contention that microangiopathy is genetically predestined [2]. If GBM thickening occurs only in diabetics who are hyperglycemic, then even though a tendency toward hyperglycemia is inherited, microvascular disease may not be inevitable.

Table 1. Diabetes-induced renal disorders

Infectious
Bacteriuria
Pyelonephritis
Renal carbuncle
Toxic
Contrast media-induced nephropathy
Neurogenic
Bladder atony (hydronephrosis)
Vascular
Nephrosclerosis
Atherosclerosis
Atheromatous embolic disease
Degenerative (idiopathic)
Diffuse intracapillary glomerulosclerosis
Nodular intracapillary glomerulosclerosis

Viberti recently reviewed the renal functional alterations in type-I diabetics that can be detected years before nephropathy becomes clinically evident [3]. Patients with newly diagnosed type-I diabetes [4] and adults with long-standing type-I disease [5] have supranormal glomerular filtration rates, approximately 140% of that of age- and sex-matched nondiabetic control subjects. Although renal plasma flow originally was thought to be elevated in patients with type-I disease [4], recent studies show it to be either unchanged or depressed in the patients with an increased GFR [5]. The elevated GFR is partially corrected when hyperglycemia is first regulated, although supranormal values persist for at least the first decade of insulin dependence [6].

Proteinuria is the first sign of glomerular damage. Type-I diabetics without proteinuria after 5 to 10 years can be provoked to excrete protein by treadmill exercise or other stress that does not cause proteinuria in nondiabetics [7]. Depending on the technique used for measurement, the prevalence of proteinuria has been reported to be as high as 100% in type-I diabetics after 6 months to 39 years of insulin use in one study [7], or less than 10% in the first 10 years in another study [8]. Newly diagnosed type-II diabetics have constant urinary albumin excretion as shown by Keen et al [9], but type-I diabetics at the onset of their disease are proteinuric only when in poor metabolic control [10]. This difference may reflect the presence of nephrosclerosis in older type-II diabetics who may have had years of previously undetected carbohydrate intolerance. Further study of the influence of exercise on proteinuria in diabetes is likely to be fruitful. We know that the amount of postexercise proteinuria is determined both by the basal protein excretory rate and the intensity of exercise. Exercise-induced proteinuria in diabetics without proteinuria at rest might be the first clue to glomerulosclerosis.

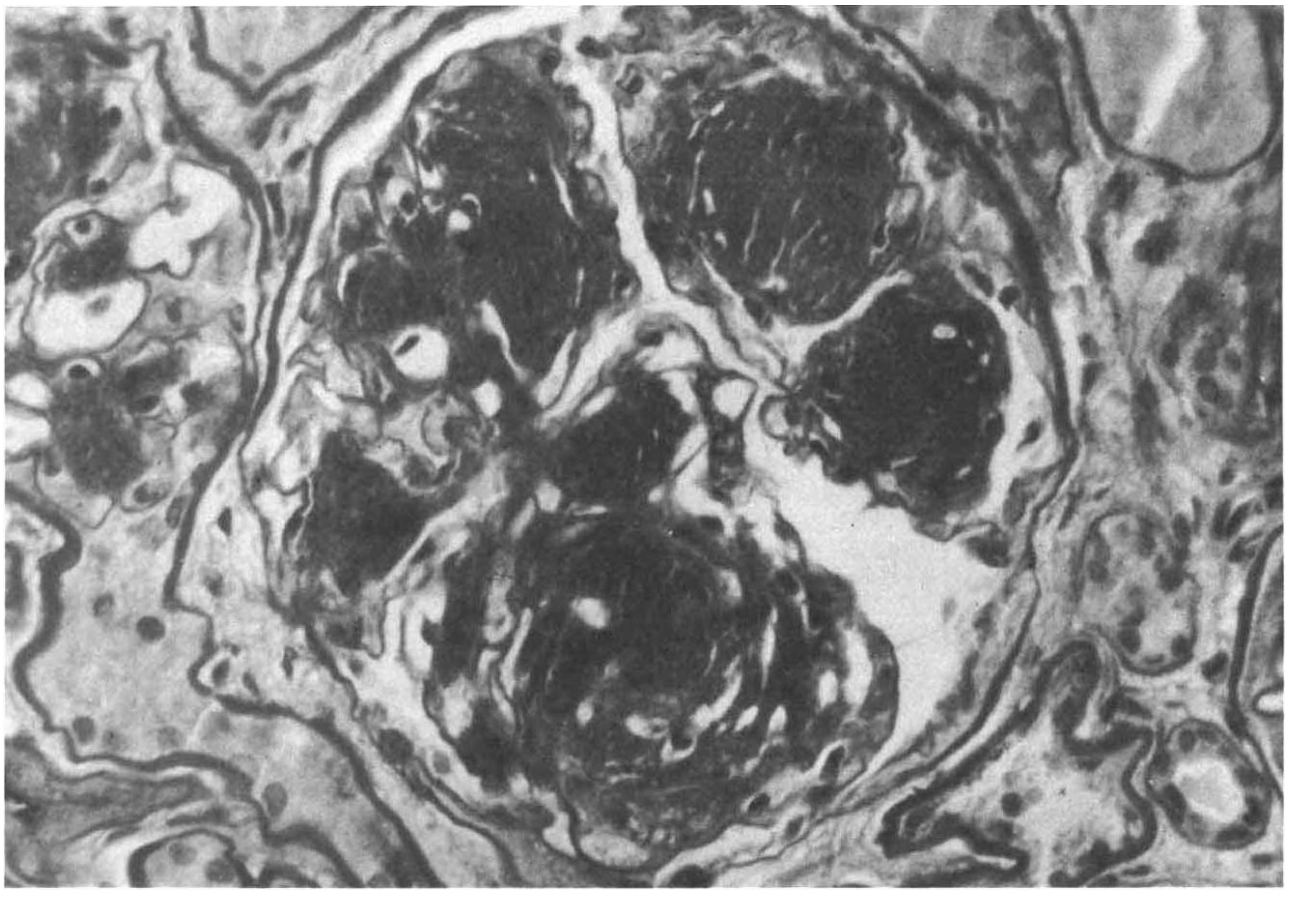

Fig. 1. *Nodular intercapillary glomerulosclerosis.* Advanced stage in type-I diabetic after 19 years of insulin use. Almost total obliteration of capillary loops has taken place accounting for a serum creatinine concentration of 11 mg/dl.

The proportion of type-I diabetics who exhibit proteinuria increases steadily as a function of duration of insulin dependence. By the 20th year of insulin treatment, about one-half of patients have continuous proteinuria [12]. Fixed proteinuria is an ominous sign; according to Mogenson, in diabetics with fixed proteinuria and a normal GFR, the GFR will subsequently decline at the rate of approximately 11 ml/min/year [13]. An elevated serum creatinine concentration follows the appearance of proteinuria by an average of about one year, although there is wide variability. Some patients maintain a normal serum creatinine level after 5 or more years of proteinuria [14]. Urinary protein losses can exceed 10 to 20 g/day and result in hypoproteinemia and a typical nephrotic syndrome.

Other than fluid retention, there are few clinical consequences of the nephrotic syndrome secondary to glomerulosclerosis. Nevertheless, in my experience, nephrotic diabetics appear sicker than nondiabetics with proteinuria of equivalent degree. Indeed, the diabetics are often cachectic. Diabetics retain extracellular and intravascular fluid at serum albumin levels that do not induce fluid accumulation in nondiabetics. Fluid overloaded diabetics with glomerulosclerosis may have a serum albumin concentration of 2.8 to 3.4 g/dl. Whether marginal cardiac decompensation or more permeable capillaries are responsible for this phenomenon remains to be clarified.

According to a study by Rutherford et al, azotemia supervenes in type-I diabetics after a mean of 17.3 years of insulin dependence; there follows an exponential decline in renal function that lasts a mean of 3 years [15]. The rate of loss of GFR is relatively constant for each patient and forms a straight line when the reciprocal of the serum creatinine concentration is plotted against time [16]. Glomerulosclerosis usually takes 20 years to progress from initiation of insulin dependence to the onset of uremia (Fig. 3). This patient's kidneys failed 22 years after he received his first insulin dose; glomerulosclerosis was the predictable finding at necropsy.

Recently, the belief that renal insufficiency was the inevitable and unavoidable consequence of long-duration, type-I diabetes has been replaced by growing excitement over the possibility that vigorous therapy might retard progression of glomerulosclerosis. This view has been nurtured by two clinical observations: (*1*) aggressive reduction of blood pressure in hypertensive type-I diabetics with renal insufficiency slows deterioration of GFR, as shown by Mogenson [17]; and (*2*) in large but uncontrolled clinical trials of strict regulation of blood glucose concentration, Cahill has noted a substantive decline in the rate of development of uremia [18].

Management of uremia. Management of the uremic diabetic patient entails more than treatment of renal failure. Nearly all type-I diabetics have serious retinopathy when renal insufficiency first develops; in fact 50% are blind or have lost some

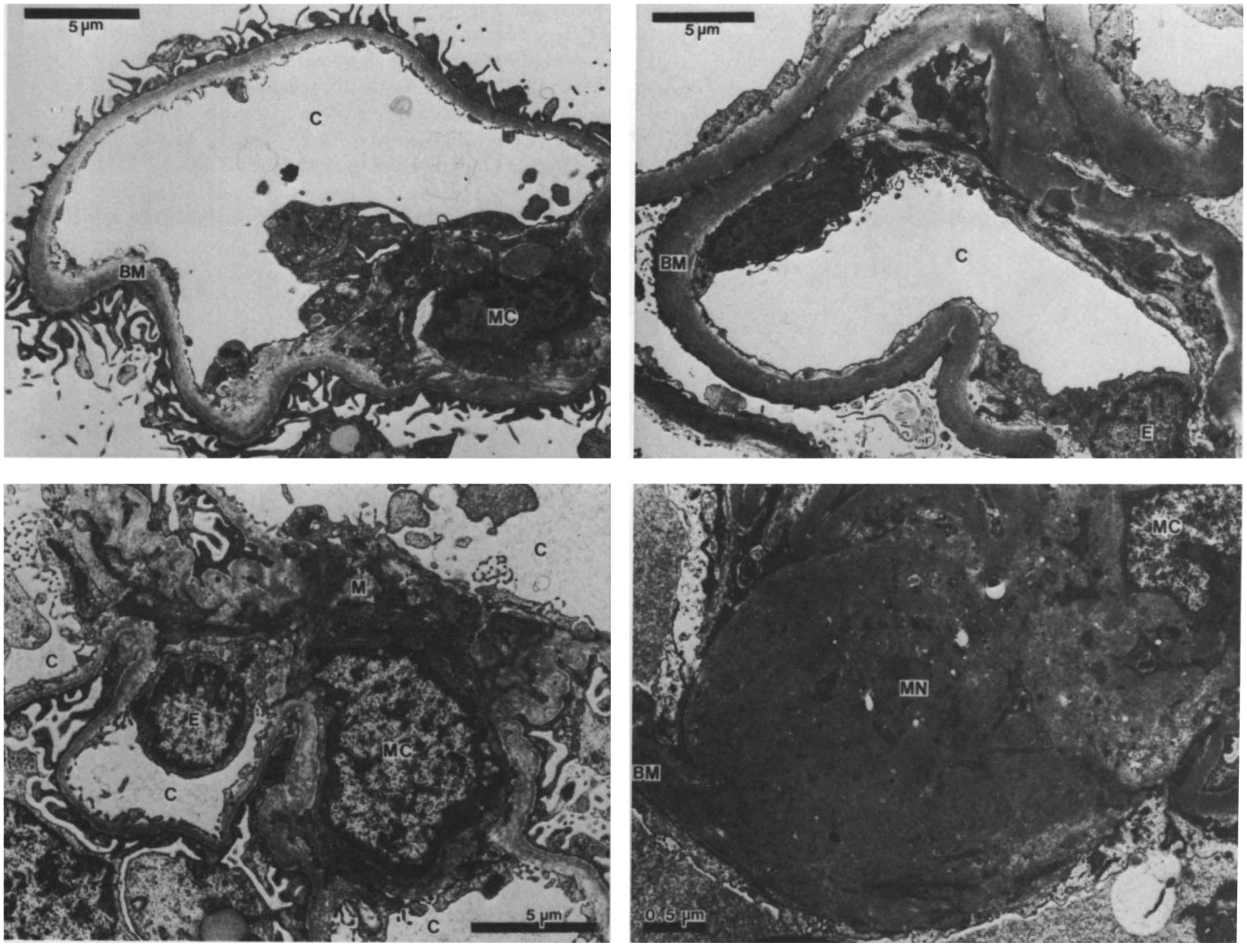

Fig. 2. *Mesangial and basement membrane changes of diabetic nephropathy.* Composite electron photomicrograph contrasting normal and diabetic changes. Upper left shows normal glomerular basement membrane (BM) with finger-like epithelial foot processes in nondiabetic adult. Upper right shows thickened, dense glomerular basement membrane and fused foot processes after 11 years of type-I diabetes. Lower left shows normal mesangial (M) region of glomerulus in nondiabetic adult. Lower right shows that early nodular glomerulosclerosis located in mesangium nodule (MN) is composed of mesangial matrix with remnants of mesangial cell (MC) debris in type-I diabetic adult after 11 years. C indicates capillary lumen; E indicates endothelial cell.

vision [19]. The coexistence of renal insufficiency, cataracts, glaucoma, and, most important, proliferative retinopathy with retinal and vitreous hemorrhages comprises what we have termed a "renal-retinal syndrome." Collaboration with an experienced ophthalmologist is vital for optimizing rehabilitation of uremic type-I diabetics. The combination of properly timed laser therapy (panretinal photocoagulation) and extraction of clot and fibrous tissue from the vitreous chamber (vitrectomy) now allows the majority of insulin-dependent diabetics to retain adequate (ambulatory) vision throughout their course, as did today's patient. Many patients also require medical attention for coincident sensory and motor neuropathy, peripheral vascular insufficiency, inadequate cerebral perfusion, and deterioration in myocardial function.

As uremia becomes the dominant clinical problem, patients and their families often despair and may even panic unless a therapeutic strategy has been devised in advance. Prior to their referral to a nephrology program, azotemic type-I diabetics typically have been managed solely for their eye problem or for their heart failure by subspecialists who fail to communicate with each other. As a consequence, the patient may be given conflicting opinions about the optimal diet and may be given drugs that have adverse interactions. By the time uremia becomes manifest, the type-I diabetic may be forced to spend much time and money traveling from one subspecialist to another.

Optimal management of uremic diabetics by dialysis or renal transplantation requires development of a team plan in which a single physician, clearly identifiable as the patient's doctor, follows through in integrating needed services. Full disclosure of available therapeutic options and the chances of success fortifies the patient against future stresses. In managing progressive glomerulosclerosis, special attention must be directed at (*1*) avoiding iatrogenic renal injury by limiting the use of

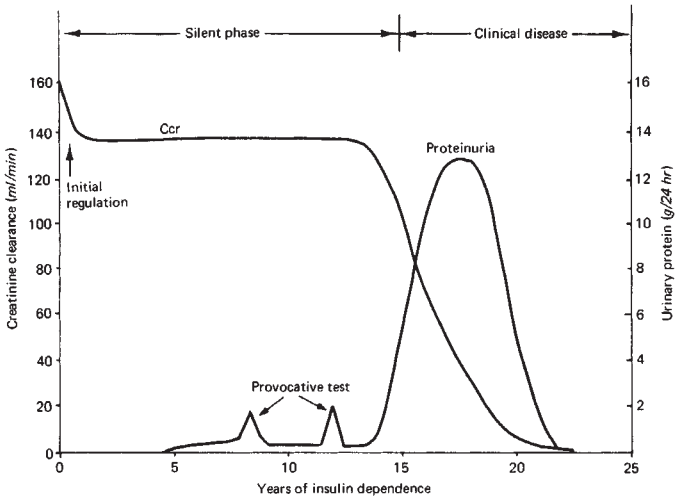

Fig. 3. *Natural history of diabetic nephropathy.* Note that a normal or supernormal GFR is usual throughout most of the course of type-I diabetes. Proteinuria typically precedes azotemia. The interval between onset of insulin dependence and end-stage renal failure is typically 20 years.

contrast media, nephrotoxic drugs, and urethral instrumentation; (*2*) controlling hypertension; (*3*) monitoring cardiac status; (*4*) manipulating protein, sodium, and caloric intake in recognition of the changing but conjoint constraints of diabetes and renal insufficiency; (*5*) adjusting insulin dose downward as renal disease worsens; and (*6*) as in all patients with advancing renal failure, minimizing uremic osteodystrophy by appropriate treatment of altered phosphate and calcium metabolism.

As renal reserve declines, a decision must be made regarding therapy beyond conservative care (Tables 2 and 3). For the nondiabetic, dialysis usually can be safely delayed so long as the GFR exceeds 5 ml/min. By contrast, type-I diabetics are often severely symptomatic when the GFR falls to 10 ml/min, and therapy must be started earlier (personal observation). Little information was provided about this patient's pretransplant therapeutic regimen other than that he responded well to treatment for hypertension and cardiac failure. The protocol does not distinguish between actual myocardial failure and volume overload. My guess is that fluid retention and hypertension contributed more to the patient's illness than did true cardiac failure.

The first decision to be made by the uremic diabetic patient is whether to be treated at all for renal failure. A blind, hemiparetic, double amputee might, after discussion with the family, decline the chance for a few additional months or years of life on the grounds that there is little likelihood of enjoyable life even with the best-imagined result. Informed uremic diabetics who do opt for aggressive treatment can be offered a variety of very different therapies, all of which can extend life under some circumstances (Tables 2, 3, 4).

Dialysis in diabetic patients. Repetitive hemodialysis for diabetic nephropathy, first attempted by Avram [20], has become the most frequently used method for sustaining life in type-I diabetics. In the early 1970s, the annual mortality for hemodialyzed patients with type-I disease exceeded 60%, and 50% of the surviving patients became blind [21]. By the end of that decade, however, appreciation of the importance of control of hypertension and intravascular volume overload improved the lot of dialyzed patients, half of whom now live for at least 3 years [22]. Still, it is disturbing that fewer than one in four hemodialyzed diabetics is able to return to work, school, or home responsibilities [23]. Great Britain and other countries with underfunded health care systems consider the outlook for hemodialyzed diabetics so poor that such patients are excluded from treatment [24]. In our experience, however, some hemodialyzed, type-I diabetics do work, raise families, and lead vigorous lives, thus precluding a pessimistic prediction for every diabetic who is about to begin dialysis.

Yet it is true that even in series with the best results, survival of type-I diabetics 2 years from the initiation of dialysis is about 20% worse than that for nondiabetics [22]. Death in hemodialyzed diabetics usually is caused by cardiovascular disease (30% to 70% of patients). Cerebrovascular accidents, infection, and uremia or withdrawal from dialysis each account for about 15% of deaths. After the failure of a kidney transplant, uremia was treated in the patient under discussion by maintenance hemodialysis. The extremely depressed dialysis patient may give up, pay little attention to dietary or fluid restrictions, become progressively withdrawn, and begin a downward spiral that may terminate in suicide. In the summary of this patient's course, no mention was made of plans for a second transplant, home hemodialysis, or some other therapeutic change that might have given the patient reason to anticipate more than his poor adaptation to institutional dialysis. For diabetics who become hypotensive during and after fluid removal by ultrafiltration, consideration of transfer to hemofiltration may be advisable [25]. Very few diabetics have undergone maintenance hemofiltration, but the initial experience is encouraging.

In early 1982, approximately 6000 Americans were being treated for uremia by peritoneal dialysis. As a group, type-I diabetics have not responded well to intermittent (thrice weekly) peritoneal dialysis; these patients have achieved one-year survival rates of only 22% to 50% [26]. Limited survival probably results from extreme hyperglycemia induced by dialysate glucose concentrations of 1500 to 4500 mg/dl and fluid retention. More recently, the combination of CAPD and the addition of insulin to dialysate, as suggested by Crossley and Kjellstrand [27], has substantially increased the one-year survival to more than 80% [28]. Advantages of CAPD over hemodialysis include rapid training (under one week), lack of need for a recycling machine, minimal cardiac stress, and superior blood glucose regulation. Trials now in progress will ascertain whether these advantages will outweigh the difficulties that stem from recurrent peritonitis and from the enervation related to a seven-day-a-week therapeutic regimen.

Transplantation in diabetics. In my opinion, kidney transplantation has emerged as the preferable therapy for type-I diabetics. A functioning renal allograft permits a degree of rehabilitation unobtainable by even the best hemodialysis. Until the past 3 years, however, one's chance of dying despite receiving a cadaveric kidney (35% in 2 years) discouraged many informed uremic patients from choosing transplantation over dialysis. For the type-I diabetic who typically experienced a series of disasters on dialysis, as did the patient under discussion today, the decision to "try a transplant" is less difficult. In such patients, the choice often appeared to be

Table 2. Selecting optimal therapy for diabetics with uremia

	Advantages	Disadvantages
Renal transplantation	Cures uremia for duration of graft function Stabilizes retinopathy Permits long intervals (months) away from treatment facility Reverses neuropathy Best rehabilitation Long-term survival	Steroids complicate glucose control Risk of infectious complication High mortality in cadaveric graft recipients Risk of developing diabetes in familial donors Not applicable to elderly or patients with cardiovascular instability Gomerulosclerosis can recur
Peritoneal dialysis	Avoids major surgery Minimizes burden on cardiovascular system Facilitates glucose regulation when insulin is added to dialysate Adaptable to home care (intermittent PD or CAPD) in selected patients	High mortality Retinopathy progresses Limited long-term success
Hemodialysis	Avoids major surgery Permits care by experienced staff Available in most countries	Poor rehabilitation Retinopathy may progress Mortality equivalent to that for cadaveric graft recipients Inexorable "failure to thrive" syndrome in about 25% of patients

Table 3. Suggested therapy in uremic diabetic patients

Age range *(years)*	Renal transplant	Peritoneal dialysis	Hemodialysis
18 to 44	++[a]	?	+[b]
45 to 65	Selected patients	+	+
Over 65 (or presence of intractable heart failure)	−[c]	+	+

[a] ++ refers to strongly recommended, especially if family donor available
[b] + refers to recommended
[c] − refers to not recommended

between kidney transplantation and imminent death. Najarian appreciated this dilemma even though he collaborated with nephrologists who provided excellent hemodialysis [29, 30]. Gradually, a combination of azathioprine, prednisone, antithymocyte globulin, and splenectomy was devised that much improved the prospects for uremic patients undergoing transplantation: one recent series of cadaveric allografts in type-I diabetics produced an astonishing 2-year functional graft survival of 85% [31]. Our series, although uncontrolled, convinced me that kidney transplantation (Fig. 4) offered a better chance of life for 2 years than did hemodialysis. The posttransplant course in diabetics is associated with all the complications that occur in nondiabetics, plus a higher incidence of infection, lower limb amputation, and bladder malfunction. We have learned that diabetics need not become blind after a transplant provided that adequate vision was present at the time of kidney transplantation, and also provided that the renal allograft functions. Approximately 4 of 5 recipients will have stable or improved vision 3 years after transplantation [32, 33].

As in nondiabetics, transplantation of a well-matched kidney from a donor in the family offers the best chance of survival and ultimate rehabilitation. For a kidney transplanted from a haplotype-identical sibling to a type-I diabetic, the 2-year patient survival exceeds 80%, with graft function in about 70% [30]. A cadaveric kidney offers the next best chance for rehabilitation. Cadaveric graft recipients do not survive as long as do patients who receive kidneys from a sibling; about 60% live 2 years, with graft function in about 50%.

Tables 2 and 3 compare key factors governing selection of treatment for a type-I diabetic with end-stage renal disease. Not all clinicians would concur with my preference for a transplant. Kjellstrand, for example, emphasized a recent improvement in the survival rate for hemodialysis patients and attributed this success to more vigorous control of hypertension and volume overload; he argued that in many instances hemodialysis is preferable to a cadaveric renal transplant [34].

Returning to our patient, we note that although he received a "perfect" 4 antigen matched cadaver kidney, it functioned for only 14 days and was lost to a vigorous rejection episode despite graft irradiation and high doses of steroids. This kind of experience confirms our own suspicion that the matched HLA antigens comprise only part of the antigen system that determines our individuality. Graft survival at one year in the best and worst HLA-matched donor-recipient pairs (in cadaveric transplantation) in this country probably differs by no more than 10%.

The history of prior blood transfusions was not included in the case description, but this information is vital for assessing transplant results. Opelz and Terasaki initially detected the effect of blood transfusions: graft survival is directly proportional to the number of transfusions the patient has received prior to cadaveric transplantation [35]. Graft recipients who have received 10 or more transfusions show an approximately 20% greater rate of graft retention at one year than do untransfused patients of the same age and sex. Since numerous groups have confirmed the benefit of transfusion, many transplant centers prescribe elective pretransplant transfusions in the 2 months before a dialysis patient is placed on an active recipient list. Potential recipients of a kidney from a living related donor against whom there is a strong mixed lymphocyte reaction may benefit from pretransplant donor-specific blood transfusions. Feduska et al used donor-specific transfusions in 20 type-I uremic diabetics and found that 3 patients (15%) developed

Table 4. Comparison of diabetic control before and after close monitoring of blood glucose and split doses of insulin

Age of patient	Therapy	Daily glucose before *(mg/dl)*	Daily glucose[a] after *(mg/dl)*	Hemoglobin A_1c before	Hemoglobin A_1c[b] after
35	Transplant	181–350	100–180	—	—
48	Transplant	31–152	100–180	9.0	7.0
37	Transplant	96–314	80–80	9.3	6.8
51	Transplant	280–612	120–120	7.9	7.0
41	Transplant	96–224	110–120	10.5	9.7
54	Hemodialysis	160–375	80–180	12.9	8.1
54	Hemodialysis	78–162	80–120	9.1	6.8
44	Hemodialysis	192–495	150–180	10.8	9.4

[a] Determined by Chemstrip
[b] Lowest value achieved during 6 months of self-monitoring

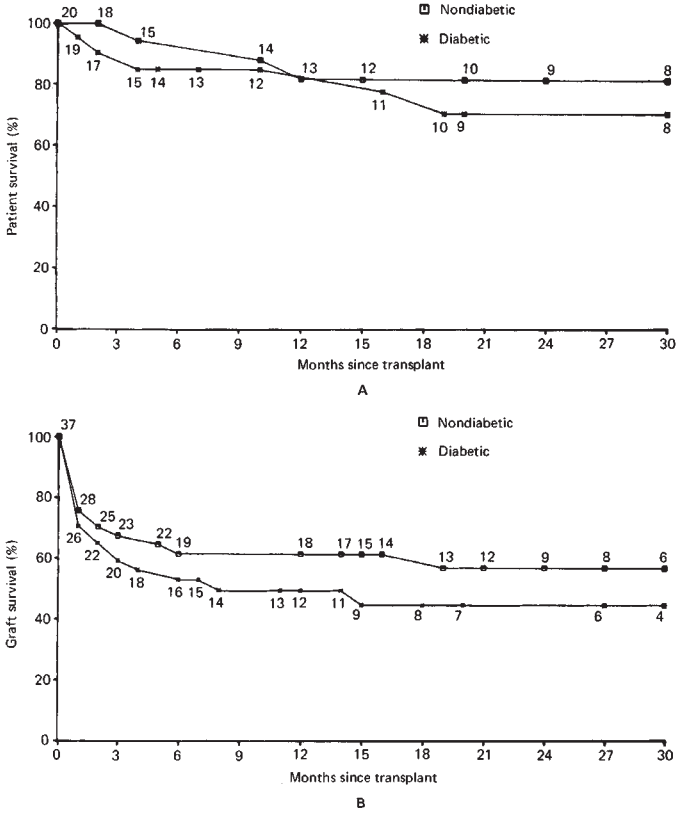

Fig. 4(A) *Kidney transplants in diabetics.* Actuarial plot of survival of patients with renal grafts from living related donors at Downstate Medical Center for the past 2 years. Mortality in diabetic recipients is about 11% greater at 2 years than in nondiabetics (courtesy Dr. K. M. H. Butt). **(B)** *Cadaveric graft function in diabetics and nondiabetics at Downstate Medical Center.* At 2 years, about 50% of diabetics retain their grafts, but as a group these patients do less well than do nondiabetics (courtesy of Dr. K. M. H. Butt).

antileukocyte antibodies against the donor, thus precluding use of a graft from that individual [36]. Of 16 patients who subsequently received a kidney from their blood donor, graft survival was 93% and 84% at 1 and 3 years respectively.

Diabetics are exceptionally vulnerable to the toxic effects of large doses of methylprednisolone, which often are administered to reverse graft rejection. Cyclosporin A [37] and monoclonal antibody against thymus-derived lymphocytes [38], both newer immunosuppressive agents that permit the use of lower doses of steroid than does azathioprine, have elicited great interest for their potential value in diabetic renal graft recipients. In 1982, state-of-the-art immunosuppression should permit greater than 50% of cadaveric kidney grafts to function for at least 2 years in optimally treated type-I diabetics.

Rationale for close control of blood glucose levels. I would like to close with the reasoning behind my contention that glucose regulation should be the pivotal component in any strategy for diabetic management, irrespective of the patient's renal function. Over the past 3 years, much has been learned about possible mechanisms by which hyperglycemia can induce glomerular injury, and considerable evidence indicates that keeping blood glucose within the normal range can be protective. Fast hemoglobin, also termed hemoglobin A_1c, is a form of hemoglobin synthesized in proportion to the time-averaged blood glucose concentration [39]. Hemoglobin A_1c, which can be measured in a commercially available, disposable chromatography column, can be used as a guide to insulin therapy. Also marketed recently are simplified reagent strips that permit patients to measure their own blood glucose levels several times daily. Guided by frequent glucose determinations, multiple-dose [40] or continuously infused [41] insulin regimens have approached Elliot Joslin's visionary ideal of an insulin-dependent patient who is euglycemic around-the-clock.

Observations made in nearly eugylcemic, type-I diabetics force revision of our concepts about what is and what is not an inherent (genetic) part of diabetes. With blood glucose levels kept within normal limits, virtually every aspect of altered metabolism in the diabetic—from hyperlipidemia to abnormal activity of counterregulatory hormones—is corrected. Euglycemic pregnant women with diabetes have babies without polyhydramnios or neonatal distress [41]. At least 100 papers now support the argument that a sustained normalization of blood glucose is good for the type-I diabetic both biochemically and clinically. But what effect does euglycemia have on the glomerulus in a diabetic patient?

The rat with streptozotocin-induced diabetes, like the human with type-I diabetes, develops increased kidney, glomerular, and mesangial size; these changes can be prevented or corrected by insulin treatment or islet of Langerhans transplants [42]. When rat kidneys with histopathologic glomerular changes similar to glomerulosclerosis are transplanted into nondiabetic, isogeneic recipients, glomerulopathy is reversed [43]. Critics have disparaged conclusions drawn from these experiments

because of the differences in appearance of rat and human glomerulosclerosis. In 1981, however, two experiments performed in Minneapolis added credence to the postulate that hyperglycemia causes glomerulopathy. In the first study, Mauer showed that when blood sugar levels are rigorously controlled in type-I diabetic recipients of nondiabetic donor kidneys, recurrent glomerulosclerosis is delayed or avoided [44]. In the second study, Najarian observed that glomerulosclerosis regressed after pancreatic transplantation in a diabetic patient who had received a kidney transplant from a nondiabetic donor and had developed recurrent glomerulosclerosis in the graft [45].

How can a nephrologist use the hypothesis that diabetic nephropathy is a glomerulopathy resulting from hyperglycemia? I believe the responsible physician should initiate an intensified effort to achieve euglycemia in all diabetics with renal insufficiency. There is little reason to consider abnormally wide swings in blood glucose any less undesirable in diabetics with failed kidneys than in patients without azotemia. Indeed, one could hypothesize that an explanation for reduced survival in diabetics treated by hemodialysis and kidney transplantation is poor regulation of blood glucose. Representative blood glucose levels in a conventionally controlled type-I diabetic on hemodialysis (Fig. 5) and a type-I diabetic recipient of a cadaveric kidney (Fig. 6) illustrate the usual extent of inadequate glucose regulation. We conducted a pilot study of "tight" glucose control in 5 renal transplant recipients and 3 hemodialysis patients; we used split insulin doses and had the patients monitor their blood glucose levels [46]. Improved control was confirmed by a reduction in hemoglobin A_1c (Table 4). In principle, incorporation of a tight glucose control plan in the care of type-I transplant recipients should prove salutary in two important ways: *(1)* All the subjective benefits of euglycemia noted in nonazotemic diabetics should be realized; and *(2)* Euglycemia might protect the renal transplant from recurrent glomerulopathy.

It is reassuring to those about to embark on trials of tight control of blood sugar in diabetic renal transplant recipients that careful glucose regulation after kidney transplantation does not seem to impose any negative consequences.

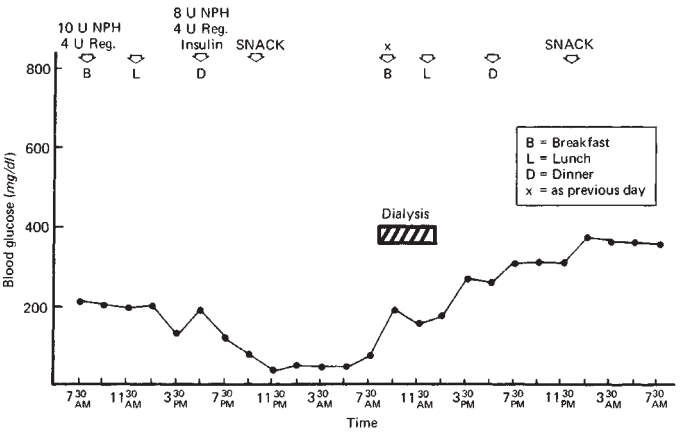

Fig. 5. *Diabetic on hemodialysis.* Glucose control by conventional therapy is poor in this uremic 43-year-old type-I diabetic woman. None of the diabetics whose glucose level was monitored during a dialysis day had what could be termed satisfactory control. Note severe hypoglycemia at 11:30 P.M. on day 1 (courtesy C. S. Levitz).

Questions and answers

DR. JOHN T. HARRINGTON: Before nirvana arrives when all blood sugars are normal and we don't have patients with diabetic nephropathy anymore, we still have enormous problems to deal with. How do you decide, in an individual patient, among the various options available for the diabetic patient with total renal failure?

DR. FRIEDMAN: As is true for the nondiabetic uremic patient, no single therapeutic approach is endorsed by physicians treating diabetics with total renal failure. To illustrate this point, it is instructive to observe the difference of opinion between medical and surgical members of the transplantation team at the University of Minnesota, the institution with the largest and most scholarly experience in treating diabetics with uremia. Najarian, who is surgeon-in-chief, cites his most recent series of cadaveric transplants in type-I diabetics to support his contention that renal allografting is the treatment of choice: a remarkable 85% 2-year functional graft survival was achieved [31]. On the other hand, Kjellstrand, who directed medical management (including hemodialysis) for Najarian's patients, calculated that his latest series of type-I diabetics on maintenance hemodialysis had a higher survival rate than did a reported series of cadaveric kidney recipients [34]. The absence of any age-matched prospective trial of alternate patients treated either by dialysis or transplantation precludes a definitive answer as to which offers better survival rates. My guess is that the greatest chance of living 5 years is offered by a related donor transplant. Lacking such a donor, survival after a cadaveric kidney graft is probably worse in the first year than for a year of maintenance hemodialysis. Three years later, I believe that there is probably little difference in the survival rate afforded by the two treatments. Information as to which option yields more complete rehabilitation is sketchy, although my experience indicates that when a transplant functions, the diabetic attains a level of well-being unreachable by dialysis. Whether CAPD will become an appropriate option remains to be seen.

Although I like to believe that my patients exercise free will in selecting their therapy, I recognize the difficulty in obtaining truly informed consent [47], and I usually communicate my bias as to which option I prefer. For type-I diabetics under 50 years of age, a living donor transplant is my first choice, followed by a cadaveric kidney graft and, last, hemodialysis performed at home. Older patients are started on dialysis and transferred to the transplant group should they deteriorate or fail to improve on dialysis.

DR. HARRINGTON: You mentioned in passing that there is some new information about the efficacy of CAPD in diabetic patients. Could you elaborate?

DR. FRIEDMAN: A major potential advantage of CAPD in diabetics is reduced stress on a heart often affected by cardiomyopathy. Whereas only 2 years ago, the 2-year mortality rate for type-I diabetics treated by intermittent peritoneal dialysis was greater than 65%, Oreopoulos [48] and Flynn in separate trials of CAPD now in progress have been able to keep over 50% to 60% of patients alive for at least 2 years. Both teams believe that the addition of insulin to dialysate eases diabetic control and permits tolerance of the large glucose load present

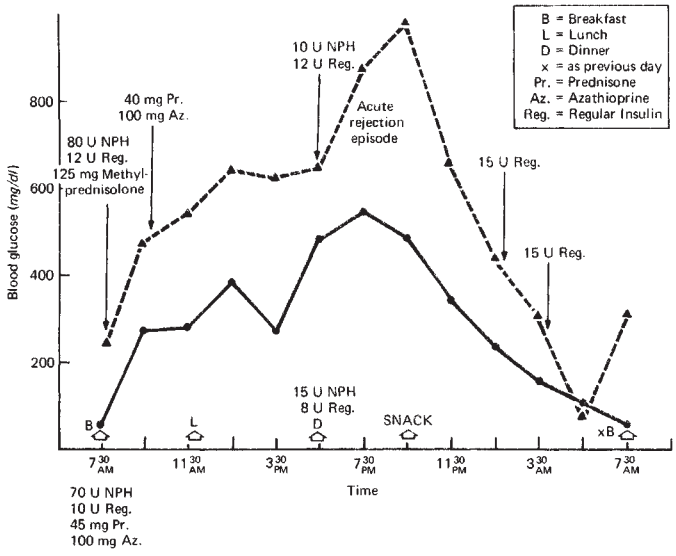

Fig. 6. *Diabetic renal transplant recipient.* This 42-year-old type-I diabetic was poorly controlled on a 2-dose insulin regimen. During rejection when methylprednisolone was administered, plasma glucose concentration reached 1100 mg/dl (courtesy C. S. Levitz).

in dialysate at concentrations of 1500 to 4500 mg/dl. Should these favorable results continue, the proportion of type-I diabetics treated by CAPD can be expected to rise substantially.

Intraperitoneal infusion of insulin may promote a more nearly normal glucose metabolism than do either the subcutaneous or intravenous routes. Stephen, in a study in progress, is testing the hypothesis that continuous intraperitoneal infusion of insulin even may prove beneficial to type-I diabetics prior to the development of end-stage renal disease. After 6 months, Stephen has noted sustained euglycemia, good patient acceptance, and a reduction in daily protein excretion. Within 3 years, I anticipate that sufficient data will be in hand to provide for a more precise response as to the place of CAPD as therapy for uremic diabetics.

DR. SANG CHO *(Chief, Transplantation Service, NEMC):* In our transplantation program, we haven't used the kind of tight control of blood sugar you have talked about in diabetic recipients. Are there any data indicating that the rate of progression of the vascular disease is faster in diabetic patients receiving hemodialysis than in those who have a functioning kidney transplant?

DR. FRIEDMAN: Serious vascular disease can progress in both hemodialyzed and transplanted diabetics. Amputation of a digit or limb is required in about 15% to 20% of transplant recipients [49], but only in about 5% of dialysis patients. There is no study quantifying the relative risk of stroke, heart attack, and limb loss with both therapies. My impression is that more transplant recipients suffer limb loss, especially of the lower extremity, whereas more dialysis patients suffer stroke and heart attack.

DR. CHO: As newer forms of immunosuppression come along, such as cyclosporin A and monoclonal antibodies [38], we will almost certainly, as you suggested, depend less on steroids than we do now. That may change our view of the benefit of transplantation in diabetic patients in the near future.

DR. FRIEDMAN: Dr. Cho, I am very enthusiastic about the imminent changes that I foresee in the transplant regimen of diabetic patients. Reviewing the changes in immunosuppression effected over the past 5 years, I have become convinced that the lesson that "less is better" has been well learned. Elimination of very large doses of methylprednisolone (1000 mg or more daily) and rapid lowering of the daily prednisone dose to 30 mg or less by the second posttransplant month have been rewarded by increased patient survival rates with no forfeiture of graft function. If we reflect on the art of immunosuppression for organ grafting, it is instructive to appreciate that few controlled drug trials were performed and that the number of animal experiments in other than rodents is sparse. We don't know, for example, whether we can safely discontinue giving azathioprine in recipients with stable graft function after a year, or whether steroids are equally effective but less toxic if administered every other or every third day rather than daily as is our current approach. Other components of our transplantation regimen are also followed in the absence of scientific validation. To underscore this view, consider that controlled trials have not sustained the proposed rationale for giving large doses of methylprednisolone or subjecting recipients to local graft irradiation. We are pragmatists by default. Now that reports of equal graft function and better patient survival with fewer drugs are appearing, the outlook for patients should continue to improve.

DR. DONALD HRICIK *(Chief Medical Resident, NEMC):* Is there evidence in humans that strict control of hyperglycemia can reverse or retard the progression of diabetic nephropathy after renal insufficiency and progressive azotemia have developed?

DR. FRIEDMAN: There is little more than impression to answer this question. Obsolescent glomeruli will not return to life. Extrapolating from the observation that renal deterioration can be slowed by treatment of hypertension, it is tempting to infer that some partially damaged glomeruli might remain viable if protein denaturation (glycosylation) can be stopped by establishment of euglycemia. Because a few proteinuric patients begun on an insulin pump subsequently have sustained vitreous hemorrhages, we must admit that damaged blood vessels may continue to express their injury.

DR. COHEN: Would you go so far as to suggest that we could completely avoid the microvasculopathy if we could really achieve tight control of blood sugar in every diabetic?

DR. FRIEDMAN: Yes. Although other metabolic or unrecognized genetic factors might contribute to organ damage in the type-I diabetic, there seems to be little evidence to suggest that the glomerulopathy is any more than a response to glycosylation and other secondary effects of hyperglycemia. Why should this be an unreasonable hypothesis? There are numerous examples of a single metabolic defect inducing multisystem disease; Fabry's disease, cystinosis, and cystinuria immediately come to mind.

Consider how we have altered our views about the pregnant diabetic patient. By careful induction of euglycemia, all the terrible maternal and fetal complications that usually made pregnancy a disaster in such patients have been eliminated. Note further the prevention of diabetic glomerulopathy in nondiabetic human kidneys transplanted into diabetics as shown by Mauer and associates [44]. If native kidneys behave as allografted kidneys in their response to environmental

glucose, then the conclusion that diabetic glomerulopathy is a preventable disease seems inescapable.

DR. COHEN: How would you define tight control? In other words, what is euglycemia?

DR. FRIEDMAN: Restricting blood glucose variation throughout the day to a range of about 70 to 140 mg/dl is the objective of modern control regimens. We have learned from the careful monitoring of pregnant type-I diabetics that even narrower limits, of approximately 60 to 100 mg/dl, can be established for, and tolerated by, highly motivated patients.

DR. CHO: I would agree that tight control of blood glucose in the early phase of the disease might prevent the vascular complications from occurring, but it might not arrest the progression of vascular complications when tight control of blood sugar is achieved at the later stage of diabetes mellitus. A significant number of recipients of functioning pancreas transplants died of multiple vascular complications even though the blood sugar level was maintained in the normal range after pancreatic transplantation.

DR. FRIEDMAN: Gliedman's pioneer experiments in pancreatic transplantation are difficult to interpret on either side of the tight control debate. Gliedman did show that a pancreas could be transplanted and restore euglycemia [50]. It was not recognized until a decade later, however, that reduction of high blood pressure was as important to longevity as was establishment of euglycemia [17]. There has been a great resurgence of interest in pancreatic transplantation in the past 4 years because of new surgical approaches. Najarian and Sutherland have successfully undertaken a series of living related donor, segmental pancreatic transplants in type-I diabetics who were also recipients of kidney allografts [51]. Longer followup obviously is necessary for full analysis of the effects of restoration of pancreatic endocrine function. Thus far, it appears reasonable to conclude that sustained euglycemia, permitted by the pancreas graft, plus normal renal function (for one kidney) permits one to achieve nearly normal living for years. But, by no means is a vascular catastrophe unavoidable.

DR. HARRINGTON: Are there any studies of the glomerular basement membrane in young diabetics who have been treated vigorously for several years with either insulin pumps or multiple insulin injections to determine whether the anticipated basement membrane thickening is preventable?

DR. FRIEDMAN: The use of insulin pumps has been too recent for me to answer your question. Experiments are now being performed that will produce the needed data. To obtain permission for repetitive kidney biopsy of asymptomatic type-I diabetics may be difficult, of questionable ethics, and unnecessary. Other tissues are available for study, including skin and muscle capillaries. Leakage from retinal capillaries can be quantified by several techniques. Direct evidence of the value of euglycemia in protecting the kidney from glomerulosclerosis will be accumulated from serial biopsies of kidney transplants from nondiabetic into diabetic recipients. Preliminary data indicate that in the presence of euglycemia, diabetic glomerulopathy is retarded at least for the first 3 posttransplant years [52].

DR. JERRY MCCAULEY *(Research Fellow, Renal Service, NEMC):* If I understood you correctly, you seemed to suggest that hyperglycemia per se causes the complications of diabetes. Is this interpretation correct, or could it be an effect of insulin deficiency for which hyperglycemia is simply a marker?

DR. FRIEDMAN: Yours is an important question, the answer to which will provide insight into why vasculopathy results from metabolic inbalance. When I speak of hyperglycemia being harmful, I mean that glucose levels serve as a convenient indicator of the rate of tissue injury occurring in diabetics in poor control. It may very well be that high glucose concentrations cause the buildup of another product, say, glycosylated albumin, which is in fact responsible for microangiopathy. While scores of biochemical pertubations have been found in diabetics, all that have been studied revert to normal when blood glucose levels are corrected. In this context, for clinical purposes, a high blood glucose level serves as a marker of all that is wrong in the diabetic. If correcting blood glucose reverses the other changes, then whether or not hyperglycemia is the primary event is of secondary importance.

DR. MICHAEL MADAIO *(Renal Service, NEMC):* It has been suggested that the elevated GFR observed in the early phases of diabetes is in itself damaging. An analogy would be the remnant kidney model described by Hostetter and Brenner, in which an increase in single-nephron GFR is associated with the development of focal sclerosis [53]. You alluded to some data suggesting that control of hyperglycemia decreases the abnormally high GFR. Might this be a mechanism whereby euglycemia could benefit the kidney?

DR. FRIEDMAN: When type-I diabetics are initially regulated with insulin, there is a decrease in GFR, but not to normal. For at least the first decade of insulin dependence, GFR continues to be supernormal. The mechanism for the increased GFR remains unknown, although excess growth hormone and other counterregulatory hormones have been suspected as responsible. Experiments designed to directly tie the blood glucose level to GFR have been unsuccessful. The well-constructed studies of Brenner's group, yielding the inference that glomerular hyperfiltration leads to glomerulosclerosis in the rat remnant kidney, do not yet sufficiently explain the glomerulopathy found in diabetics. In a study of patients who have had type-II diabetes for 1 to more than 25 years, we found creatinine clearance to be normal or below normal no matter how long the patient had been diabetic. We interpreted these results to indicate that the glomerulosclerosis that occurs in type-II diabetes is not always the consequence of long-standing hyperfiltration [54].

DR. ANDREW S. LEVEY *(Renal Service, NEMC):* How many of your uremic or nearly uremic patients are able to achieve self monitoring and strict control?

DR. FRIEDMAN: In collaboration with Celia Levitz and Sondra Hirsch, we are now following about 25 patients who have accepted a self-monitoring blood glucose control program. Part of our study's objective is to determine how many patients will continue on the regimen "permanently."

DR. LEVEY: What are the reasons for failure among those patients? And what are the optimal methods for selecting patients to undergo this regimen?

DR. FRIEDMAN: We are beginning to form an impression of the probable limits of self monitoring for glucose levels. Neither of 2 overtly psychotic patients was able to accept the rigors of scheduled finger sticking 4 or more times daily, and both were treatment failures. Blind patients require cooperation of a family member or friend to perform repetitive testing. Transplant recipients who welcome the advantages of self monitor-

ing, which include freedom of meal timing and elimination of the need to eat "defensively" to avoid "random" hypoglycemic attacks, exhibit decreased adherence to the regimen at times of serious illnesses such as limb amputation or ocular surgery. Success in acceptance of self monitoring, with its annoying finger sticks, is a measure of patient motivation and understanding. Pregnant women, who understand that euglycemia may protect their baby, apply more than the number of tests requested and thus evince excellent complicance. Should we be able to communicate the message that euglycemia will protect their kidney transplants, many patients may be won over to the rigors of strict control.

DR. COHEN: You have made only passing reference to type-II diabetes. Are there any data to suggest that close control of blood glucose levels in these patients would have the same protective potential?

DR. FRIEDMAN: We know surprisingly little about the renal disease that complicates type-II diabetes. Although glomerular lesions apparently indistinguishable from type-I glomerulopathy occur, we can only speculate about how long they take to develop, and whether progression of microangiopathy in other organs, especially the retina, correlates to the same degree as in the type-I patient.

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